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Datasheet for the decision of 3 February 2011

Case Number: T 1696/08 - 3.3.04

Application Number: 97932311.0

Publication Number: 0954528

IPC: C07K 14/17

Language of the proceedings: EN

Title of invention:
A method for chromatographic removal of prions

Patentee:
BIOPURE CORPORATION

Opponent:
Octapharma AG

Headword:
Removal of prions/BIOPURE

Relevant legal provisions:
EPC Art. 56

Keyword:
"New main request - inventive step (yes)"

Decisions cited:
T 0939/92

Catchword:
-

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Case Number: T 1696/08 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 3 February 2011

Appellant: (Opponent)
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Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted 7 July 2008 rejecting the opposition filed against European patent No. 0954528 pursuant to Article 101(2) EPC.

Composition of the Board:

Chairman: C. Rennie-Smith
Members: M. Wieser
B. Claes

Summary of Facts and Submissions

I. An appeal was lodged by the Opponent (Appellant) against the decision of the Opposition Division according to which the opposition against European patent No. 954 528 was rejected (Article 101(2) EPC).

II. The patent, which had been granted with a set of ten claims, had been opposed under Article 100(a) EPC for lack of inventive step (Article 56 EPC).

Claim 1, the only independent claim, read as follows:

"A method of removing a prion from a solution comprising the prion and an additional protein, comprising the step of directing the solution through an anion exchange chromatography column under conditions that cause a pH gradient elution, whereby the prion is separated from the additional protein, thereby causing said protein to be collected in an eluate fraction that is distinct from the eluate fraction that includes the prion."

III. The Opposition Division decided that the subject-matter of claims 1 to 10 as granted involved an inventive step and met the requirements of Article 56 EPC.

IV. The Board expressed its preliminary opinion in a communication dated 26 July 2010. Oral proceedings were held on 3 February 2011.

The Appellant requested that the decision under appeal be set aside and that the patent be revoked.

The Patent Proprietor (Respondent) requested that the decision under appeal be set aside and that the patent be maintained on the basis of claims 1 to 9 of its new main request filed at the oral proceedings.

V. Claim 1 of Respondent's new main request read as follows:

"A method of removing a prion from a solution comprising the prion and hemoglobin, comprising the step of directing the solution through an anion exchange chromatography column under conditions that cause a pH gradient elution, whereby the prion is separated from the hemoglobin, thereby causing said hemoglobin to be collected in an eluated fraction that is distinct from the eluate fraction that includes the prion."

Dependent claims 2 to 9 referred to preferred embodiments of the method of claim 1 and were identical to clams 2 to 5 and 7 to 10 as granted, with the only exception that the back-references in claims 6 to 9 (granted claims 7 to 10) have been adapted to the new numbering.

VI. The submissions made by the Appellant, as far as they are relevant to the present decision, may be summarised as follows:

Document (2) at least provided evidence that some separation of prions and additional proteins was possible by anion exchange chromatography under conditions causing a salt gradient. The skilled person, knowing that a pH gradient was the only available

alternative to the use of a salt gradient, would have tried this possible method and would have arrived at the claimed subject-matter in an obvious way. Therefore, even if the obtained result had to be considered as surprising, it did not involve an inventive step.

VII. The submissions made by the Respondent, as far as they are relevant to the present decision, may be summarised as follows:

In the light of the ineffective experiments described in document (2) the skilled person had no reason to consider that prions and hemoglobin could successfully be separated by anion chromatography. The various prion isoforms with isoelectric points (Ip) in the range from 4.6 to 7.9 formed polymers whose behaviour in an ion chromatographic column was highly unforeseeable. Since the Ip of haemoglobin was known to be 6.8, its successful separation from prions by a method according to claim 1 was highly surprising and far from being obvious.

VIII. The following documents are referred to in this decision:

(2) J. Gen. Microbiology; vol.37, 1964, pages 251 to 258

(7) A. Lehninger: Biochemistry; second edition 1970, Worth Publishers Inc., New York, pages 157 to 182

(8) J. Virology; vol.53, no.2, 1985, pages 596 to 606, abstract in PubMed

Reasons for the Decision

Amendments

1. Claim 1, when compared with claim 1 as granted, has been amended such that the "additional protein" is defined as being hemoglobin.

   This amendment does not create a lack of clarity and finds a basis in the original application, published as WO 98/00 441 (see for instance page 7, lines 10 to 34 and example 1). By defining the "additional protein" as being hemoglobin, i.e. a specific defined protein, the scope of protection of claim 1 has been restricted with regard to claim 1 as granted.

   The requirements of Articles 84, 123(2) and (3) EPC are met.

Inventive step

2. For the assessment of inventive step the Board applies the "problem and solution approach" which as a first step involves the identification of the closest prior art document. Both parties considered document (2) as representing the closest prior art. The Board agrees (see also paragraph (III) on pages 8 and 9 of the decision under appeal).

3. Document (2) describes the chromatographic behaviour of a scrapie agent from an intact and an ultrasonically treated scrapie-mouse brain mitochondrial-lysosomal fraction on DEAE-cellulose and calcium phosphate. Elution from the stationary phase was initiated by

using a salt gradient at constant pH (see page 253). Document (2) does not mention hemoglobin as being additionally contained in the examined samples.

The results of the chromatographic experiments are described on pages 254 and 255 (see especially figure 2, tables 2 and 3 and the paragraph bridging pages 254 and 255). Although a certain degree of separation of the scrapie agent from other proteins contained in the samples seems to have been achieved by some of the experimental approaches, document (2) does not report the isolation of prion-free elution fractions or, in other words, it does not show that the scrapie agent was collected in an eluate fraction distinct from the protein eluate fraction.

4. Starting from the disclosure in document (2), the problem underlying the patent in suit is regarded as being the provision of a chromatographic method of removing a prion from a solution comprising the prion and hemoglobin wherein the prion and hemoglobin are collected in different eluate fractions.

5. As a solution to this problem the patent proposes a process according to claim 1 which is characterized by directing the solution through an anion exchange chromatography column under conditions that cause a pH gradient elution.

The patent describes in example 1 (paragraphs [0032] to [0050]) the purification of a bovine hemoglobin solution by anion exchange chromatography under conditions that cause a pH gradient elution. Considering the validation of prion removal (starting

in paragraph [0051]) and the results of example 1 (see table on pages 7 and 8), the Board considers that the patent provides a technical solution to the problem it purports to solve.

6. The Board is aware of decision T 939/92 (OJ EPO 1996, 309), wherein it is stated that "[the] technical problem could only be taken into account if it could be accepted as having been solved, i.e. if, in deciding the issue under Article 56 EPC, it would be credible that substantially all **claimed** compounds possessed this activity" (third paragraph of point 2.6; emphasis added).

7. In the Board's view, the approach of decision T 939/92 is only applicable in situations where the problem to be solved consists in the achievement of an effect, which effect is not stated in the claim. Only then does the question arise whether or not all of the claimed embodiments achieve the required effect.

Present claim 1 relates to a "method of removing a prion from a solution comprising the prion and hemoglobin". Thus, the separation of the prion from hemoglobin is a feature of claim 1. Therefore, the question to be answered in the context of Article 56 EPC is not whether all the embodiments covered by the claim result in such separation since embodiments not meeting this criterion are not encompassed by the claim due to its wording. Hence, the situation underlying decision T 939/92 is different and the decision is not applicable here.

8. It remains to be examined whether the solution proposed by the patent to solve the technical problem was obvious in the light of the disclosure in the prior art documents on file.

9. The principle of ion exchange chromatography under conditions that cause a pH gradient elution relies on the fact that polar molecules can be separated based on their charge. Proteins, being amphoteric molecules containing both positive and negative charges have, depending on the pH of their surrounding environment, a specific net electrical charge.

At a pH below their isoelectric point (Ip), i.e. the pH at which a molecule carries no electrical charge, they carry a net positive charge; above their Ip they carry a net negative charge.

All molecules which, at the pH of the mobile phase, carry a net negative charge (pH above their Ip) are bound to the stationary phase of an anion exchange column. Only if two molecules have different Ips can they be selectively eluted from the stationary phase by lowering continuously or stepwise the pH of the mobile phase. When the pH is equal to the Ip of a specific molecule, it is eluted from the stationary phase and thus separated from the other molecule contained in the sample.

10. The Ip of hemoglobin is known to be about 6.8 (see document (7), page 162, table 7-1).

Isomers of the major scrapie prion protein (PrP 27-30) are known to have Ip values between 4.6 and 7.9 (document (8)).

Thus, the Ips of haemoglobin and prions are widely overlapping.

11. The skilled person trying to solve the problem underlying the patent learns from document (2) that the separation of prions from additional proteins by use of anion chromatography under conditions that cause a salt gradient elution has only limited success. Moreover he/she knows that two molecules only are considered to be separable by anion chromatography under conditions that cause a pH gradient elution if they have different Ips (see paragraph (8) above).

12. In the light of this information derivable from the prior art, the skilled person gets no hint, either from document (2), representing the closest state of the art, or from any other document on file, gets any hint to use anion chromatography under conditions that cause a pH gradient elution for the separation of two proteins, namely prions and hemoglobin, having widely overlapping isoelectric points.

13. In fact, the separation of a prion from hemoglobin by using a method according to claim 1 cannot be regarded as being obvious, rather it has to be considered as being surprising (this is also acknowledged in paragraph [0016] of the patent).

Therefore, the Board decides that the subject-matter of claim 1 and of claims 2 to 9 dependent thereon, involves an inventive step and meets the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance with the order to maintain the patent on the basis of claims 1 to 9 and pages 2 to 8 of the new main request filed at the oral proceedings.

The Registrar: The Chairman:

P. Cremona C. Rennie-Smith